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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,994	LUYTEN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-59, 61, 63 and 64* is/are pending in the application.

4a) Of the above claim(s) *31-42 and 46-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-45, 61, 63 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Remarks, filed 9/27/06, have been entered. Claims 31-59, 61, 63 and 64 are pending; claims 31-42 and 46-59 are withdrawn; claims 43, 44 and 61 are amended; claim 62 is cancelled; claims 63 and 64 are added; claims 43-45, 61, 63 and 64 are under current examination.

Election/Restrictions

Claims 31-42 and 46-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/4/05.

Applicant's election without traverse of Group XII (claims 43-45, 60 and 61) in the reply filed on 8/4/05 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-45, 61, 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A purified culture of differentiated precursor cells isolated from periosteum, bone marrow or synovial membrane, that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue, wherein the cells express CDMP-1.

The specification does not reasonably provide enablement for purified cultures of said differentiated precursor cells which express markers that are co-

expressed and/or are co-detectable with CDMP-1 and additionally are characterized by the absence of a negative marker, such as FGFR3 or another marker of the mature chondrocyte phenotype; therapeutic compositions comprising said differentiated precursor cells; implants comprising said cells; cultures of said cells that express markers that are The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the claims have now been amended to explicitly recite the source of the cells, and thus, in view of this amendment, and given Applicants' demonstration that within these tissues, only skeletal precursor cells express CDMP-1, it is submitted that the specification provides sufficient guidance to the skilled person to isolate the presently claimed cells. See page 13, 3rd ¶ of the Response.

Applicants argue that enablement of the full scope of the claimed invention does not require undue experimentation because they have demonstrated the presence of CDMP-1 as a reliable marker for skeletal precursor cells in these tissues, and that methods for isolating cell populations based upon a marker profile are known to those skilled in the art, and would not require any undue experimentation. See page 15, paragraphs 1-2 of the Response.

Response to Arguments. The enabled scope of the claimed invention is determined above. Applicants' arguments are partially persuasive, with regard to cells that are isolated from periosteum, bone marrow or synovial membrane that

express CDMP-1. In particular, the art cited for enablement in the prior Office action (Luyten *et al.*, p. 3 of the Office action, mailed 6/27/06) teaches expression of CDMP-1 in various tissues including cartilage, brain and placenta. Applicants' amendment to the claims, which now recite that the cells are isolated from periosteum, bone marrow or synovial membrane and express CDMP-1, overcome the art of Luyten *et al.* However, the prior rejections of record (advanced in the Office actions, mailed 6/27/06 and 10/21/05) are maintained and detailed below.

Applicants' arguments are only found to be persuasive with regard to CDMP-1, but not with regard to other unidentified markers that are co-expressed/co-detected with CDMP-1. Applicants have not provided sufficient guidance to other markers that are co-expressed or co-detectable with CDMP-1 such that one of skill could use these markers to uniquely identify the cell populations as instantly claimed.

Applicants' Arguments. Applicants argue that the full scope of the claims are enabled for the following reasons: 1) the cells characterized by additional markers are encompassed with the scope of independent claims 43-44, and that in addition to a positive marker, the cells of the invention can be characterized by the absence of a negative marker, such as FGFR-3. Applicants argue that the absence of a particular marker can be as important as the presence of other markers, and that the mature chondrocyte phenotype is heralded by the appear of certain markers and the absence of other makers, which further characterize the cell. See page 14, 1st ¶ of the Response.

Applicants argue that similar to co-expression, the absence of expression of a particular marker can be compare between markers, at different time points, whether positive or negative markers. Applicants argue that it is clear that a marker which is similar to FGFR-3, linked to the chondrocyte phenotype and is accordingly absent during the precursor stage of cells, is a marker that is co-expressed with the negative marker FGFR-3 and that such negative markers can be

identified when comparing the expression of mature and precursor cells. See page 14, last ¶ of the Response.

Response to Arguments. These arguments have been considered, but are not persuasive. As stated above, Applicants have not provided sufficient guidance with regard to makers that are co-expressed or co-detectable with CDMP-1. It could be envisioned that many markers would be co-detectable with CDMP-1. However, Applicants have failed to provide a sufficient nexus with regard to the particular markers that would be co-expressed/co-detectable with CDMP-1 which would allow for the isolation and identification of the skeletal precursor cells, as instantly claimed.

Furthermore, although the Examiner agrees that the absence of expression of a particular marker can help further characterize a particular cell population, the claims as now written, recite that the cells are characterized by a negative marker being FGFR3 or another marker of the mature chondrocyte phenotype. See claim 64. Although Applicants point to p. 31, lines 9-11 in their remarks, with regard to type II collagen, type X collagen, FGFR3, and BMP2, it is noted that the specification discloses other markers or factors that are co-expressed or co-detectable with these markers as negative markers as well (p. 31, lines 14-15 and p. 18, lines 1-3). Thus, the claimed breadth of other markers of the mature chondrocyte phenotype, which are used to characterize the skeletal precursor cells, are not a discrete population of markers, but other unidentified markers. Furthermore, the specification teaches that the mature chondrocyte phenotype is heralded by the expression of all of the recited markers: type II collagen, type X collagen, FGFR3, and BMP2. There is no guidance provided by the specification to show that the mature chondrocyte phenotype can be a combination of any of these markers.

Finally, it is reiterated that the absence of expression a negative marker is not within the broad scope of the claims, which require a marker that is either

expressed or detectable with CDMP-1 (see claims 43-45). A negative marker is not expressed. Claim 61 requires that the cells are characterized by the absence of a negative marker (FGFR3), or a marker or factor co-expressed or co-detectable with FGFR3. It is unclear how this would further characterize the cells, because the negative marker is not expressed, thus how could one identify markers or factors that are co-expressed with an unexpressed marker? The specification provides no guidance or teachings with regard to how to characterize cells using a negative marker (*i.e.*, one that is not expressed) or markers that are expressed in the absence of expression of the negative marker.

The other markers that are contemplated (those which are co-expressed or co-detected with CDMP-1) are not specifically taught, and one skilled in the art could not use the guidance provided by the specification to identify the cell populations. One of skill would need to practice undue experimentation to first identify these unknown markers and then determine if the marker(s) were expressed solely in the claimed cell types, or in other cell types, in order to uniquely identify the claimed cell population.

Therapeutic Benefit. Applicants argue that with regard to therapeutic benefit, the specification teaches the formation of cartilage *in vitro* using the cells of the invention (claim 6) and the enhancement of this cartilage forming ability of the chondrocytes with the cells of the invention, both *in vitro* and *in vivo*. Thus, Applicants argue, their data provide objective enablement, which is all that is required under 112, first ¶. See pages 15-16 of the Response.

Nude Mouse Model. Applicants argue that indeed, it should be realized that in practice, the treatment of humans according to the present invention will generally involve autologous cells, whereby the issue of immunocompetence is less relevant. Applicants further argue that the immunocompetence of the cells used in cellular therapy is an issue independent of the concept of the present invention, and that alternative methods exist for reducing the immunogenicity of heterologous

cells. Applicants argue that in the context of the present invention, the main issue is whether the cells of the invention are capable of producing stable hyaline cartilage upon isolation and injection into a mammal, and that this aspect of the invention is accurately demonstrated in the nude mouse model. Applicants argue that by using nude mice, it is possible to work with heterologous cells, and that this allows for the isolation of a higher number of cells (from another organism) which is comparable to the situation in humans. It is noted that the mechanisms of cartilage formation in nude mice is similar to that of wild-type mice and accordingly the evaluation of cartilage production by a cell population is routinely measured in nude mice. As taught by Applicants (see, for example, Example 7), co-implantation of freshly isolated chondrocytes with skeletal precursor cells is able to substantially reduce the number of chondrocytes needed for successful joint surface defect repair. Such co-implantation also results in a remarkable enhancement of the amount of cartilage produced. Applicants argue that the autologous chondocyte transplantation is a widely accepted technique for the repair of joint surface defects, and that this procedure has been demonstrated to effectively result in repair, but that the main limitation of this technique, prior to the claimed invention, has been the required number of cells for full repair. Applicants argue that given the fact the increased number of chondrocytes is formed using the methods of the invention, the Office has failed to provide substantive reasons why the implantation of the cell population of the present invention would fail to have therapeutic benefit. See pages 17-19 of the Response.

Response. Applicants' arguments have been considered, but are not persuasive. Given that one of skill in the art would not be able to specifically isolate the cells, as broadly claimed, using a marker co-expressed and/or co-detectable with CDMP-1, it would be unpredictable that one could use these unknown cell populations for methods of therapy. Although Applicants have postulated using various markers that might be used in these methods, as stated above, they have

not enabled using these markers (such as those co-expressed or co-detectable with CDMP-1 or FGFR3) to isolate a particular cell type, which could be used in the contemplated therapeutic methods. Neither Applicants' arguments, nor the art of record support that one could predictably isolate the claimed cells, and use them in methods of implantation for producing tissues, without undue experimentation. One of skill in the art would need to practice undue experimentation in order to isolate the cells, and then practice undue experimentation to use these cells in methods of therapy.

With regard to Applicants' statement that mechanisms of cartilage formation in nude mice are similar to that of wild-type mice, and that the evaluation of cartilage production by a cell population is routinely measured in nude mice. This is not persuasive. The arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that cartilage formation is similar between wild-type and nude mice, or that evaluation of cartilage production is routinely measured in nude mice. Furthermore, it is reiterated that the working examples fail to correlate to a therapeutic result in utilizing the claimed cells, as they are directed to injection of immunodeficient, nude mice, which would not be considered a model for an immunocompetent individual. The working example shows *in vivo* implantation of the cells by intramuscular injection of the cells into nude mice. This is not analogous to what would be considered a therapeutic treatment. For example, the specification contemplates the instant invention in the context of a mammal with cartilage defects (see page 22, lines 23-35, for example). The nude mouse, as taught in the working example, is not considered a model of cartilage defect. Furthermore, the working example only teaches the intramuscular injection of the nude mice with human skeletal precursor cells and pig articular chondrocytes. There is no teaching with regard to the injection of the instantly claimed cells in a physiologically

appropriate location, such as a joint in need of repair, to show functional rescue of the animal. Although the specification teaches that an increase in chondrocytes, this does not provide a nexus to show implantation of the instantly-claimed cells, in an appropriate model which would result in connective tissue repair, or would differentiate into cells that would integrate and function to repair the damaged or malfunctioning tissue.

Finally, although atuologous chondrocyte transplantation is a widely-accepted technique for the repair of joint surface defects, it is noted that the claims require using the skeletal precursor cells, not mature chondrocytes, in the implants or therapeutic compositions. Thus, the use of the invention in a therapeutic context would require the precursor cells to differentiate into chondrocytes *in vivo* in order to provide therapy. One of skill in the art could not rely upon the state of the art to provide this nexus, as stated in the prior Office action, because implantation of stem cells, and particularly cells that form chondrocytes or osteoblasts, that function in a physiologically appropriate manner to provide therapy, is found to be unpredictable. See pages 5-6 of the Office action mailed 10/21/05. Thus, Applicants' arguments with regard to autologous chondrocyte transplantation is not within the scope of the claimed invention, which requires the use of precursor cells for therapeutic purposes.

Hui et al. Applicants further argue that the Office's reliance upon Hui *et al.* to support the enablement rejection is improper. Applicants argue that Hui *et al.* do not show that it would not be predictable to isolate a particular cell type with makers, but that future research should be directed at better characterization fothe cells, which Applicants claim they have done. Furthermore, Applicants emphasize that the cells of the present invention are characterized as multipotent precursor cells that have entered the post-natal skeletal differentiation pathway, and such cells are not "unpredictable" as demonstrated by the *in vivo* examples found in the specification. Applicants argue further that because the claims now refer to a

specific cell type for the engineering of tissues, the reliance upon Hui *et al.* is misplaced, because Applicants have now characterized the cells as skeletal precursor cells.

Response. These arguments have been fully considered but are not persuasive. In particular, the cells, as claimed by Applicants, fail to be enabled for the reasons stated above, namely, that the markers claimed would fail to provide a unique cell population, namely with regard to cells that are identified by markers that are co-expressed/co-detectable with CDMP-1. Hui *et al.* do discuss that various markers would be useful in identifying particular cell types that would be used in methods of musculoskeletal tissue engineering. Thus, Hui *et al.* clearly show that even post-filing, it would not be predictable to isolate a particular cell type with unknown/undisclosed markers, to engineer tissues. Although Applicants' have amended the claims to recite using CDMP-1, the claims also encompass using unidentified and undetermined markers to identify the skeletal precursor cells, which are not determined to be within the enabled scope of the claimed invention for reasons stated in this and prior Office actions.

Accordingly, it is maintained that the specification fails to provide specific teachings or guidance the claimed embodiments of isolated skeletal precursor cells, because the methods taught by the specification only provide a particular marker, CDMP-1, to identify these cells. However, beyond using this single marker, the specification provides no other defining characteristics of the resultant cells. In view of the lack of teachings or guidance, with specific regard to the identification of the skeletal precursor stem cells, except by the identification of a particular marker (CDMP-1), the unpredictability in the art with regard to the intended use of the therapeutic compositions/implants for therapeutic purposes, the lack of teachings or guidance with regard to define the cells used in the working examples, the lack of nexus between the *in vivo* example, utilizing a nude, immunodeficient mouse and

any resultant therapeutic effect, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Written Description

Claims 43-45, 61 and newly added claims 63-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record advanced in the prior Office actions, mailed 6/27/06 and 10/21/05.

Applicants' Arguments. Applicants argue that the prior rejection is rendered moot in view of Applicants' amendment to the claims, which now specify the origin of the cells. Applicants argue that as for the markers that are co-expressed with CDMP-1, Applicants point to the definition of co-expression provided by the specification (p. 13, lines 17-31), wherein, Applicants claim, that co-expression is assed in the same cells as the expression of CDMP-1, so these cells do not form a separate "genus". The nature of the marker is not important, but can be "a recognizable cell surface marker, detectably via polyclonal or monoclonal antibodies and/or specific ligands." Applicants argue that it is possible, using routine experimentation, to find other markers. Further, with regard to negative markers, Applicants argue that the rejection is also rendered moot in view of the present amendment to the claims. Applicants argue that the expression of CDMP-1 is used to specifically characterize the claimed cells and provide citations throughout the specification for this support. Thus, Applicants conclude that, by the very identification of the CDMP-1 maker, they have provide guidance on how one would discern between cells that have entered a postnatal differentiation pathway, and therefore, more than adequate guidance is offered in the written description to

allow one of skill in the art to isolate the cell population as instantly claimed. See pages 19-21 of the Response.

Response to Arguments. These arguments have been considered, but are not fully persuasive. Applicants' arguments with regard to the identification of cells that have entered a post-natal skeletal differentiation pathway, the Examiner finds description with regard to utilizing CDMP-1. However, the markers that are co-expressed and/or co-detectable with CDMP-1 are not found to be described, and thus, cells that would be defined by these markers are not described. Although Applicants have now amended the claims to recite the source of the precursor cells (periosteum, bone marrow, or synovial membrane), the claims recite that the cells can be identified by CDMP-1 or, alternatively, a marker co-expressed /co-detectable with CDMP-1. It is this alternative embodiment that is found to lack a written description. MPEP §2163 clearly states that, "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." This is not dependent upon the amount of experimentation (which Applicants refer to on page 20 of their Response). Although the specification provides general guidance with regard to markers co-expressed/co-detected with CDMP-1, the specification fails to specifically describe which markers would belong to this genus. That is, one could envision that many markers would be expressed at the same time in development as CDMP-1, but the specification provides no description as to which markers would be considered indicative of uniquely identifying a population of skeletal precursor cells, as instantly claimed. These markers that are co-expressed/co-detected with CDMP-1 fail to have a written description because the specification does not describe them in sufficient detail such that one skilled in the art would recognize that Applicants had possession of the claimed invention. MPEP §2163 further states that, "Possession may be shown in a variety of ways including description of an actual reduction to

practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." In the instant case, although the specification provides general guidance on how one might ascertain if a marker were co-expressed/co-detected with CDMP-1, there is no disclosure of distinguishing, identifying characteristics of these markers, such that one of skill in the art could conclude that Applicants had possession of the markers that belong to this genus.

With regard to newly added claim 64, which now recites that the cells are further characterized by the absence of a negative marker, being FGFR3 or another marker of the mature chondrocyte phenotype, the Examiner presents new grounds of rejection, under written description, necessitated by Applicants' addition to this claim. The specification provides guidance with regard to other makers of the mature chondrocyte phenotype, which are not merely the discrete list of factors recited by Applicants in their response (see page 12 of the Response). In fact, the specification provides various places with regard to the term "negative marker", particularly, p. 18, lines 1-2, which recites FGFR3, type II collagen, type IX collagen, type XI collagen, or markers or factors co-expressed/co-detectable with these markers. It is clear from this passage that upon differentiation to chondrocytes, the expression of these markers is present (see pages 17-18, bridging sentence). Additionally, page 31, lines 9-11, recite different markers than those on page 18, namely citing type X and BMP-2 as markers that appear with regard to the mature chondrocyte phenotype. Page 31, lines 13-17 further recites using markers that are co-expressed or co-detectable with any or all these markers in order to identify the skeletal precursor cells. Thus, the phrase that recites "another marker of the mature chondrocyte phenotype" in claim 64 encompasses markers that are co-expressed or co-detectable with any of the above-recited markers. The

prior rejection of record, with regard to this aspect is maintained. As stated in the prior Office action, these markers are not described by the specification, because there is no guidance, for example, with regard to how one would identify markers that are co-expressed with a marker that is not expressed. Simply put, if a marker is not expressed, those markers that are co-detectable with it would not be able to be identified. Similarly, as stated above, the specification fails to provide sufficient description of these markers, such that one of skill in the art would recognize that Applicants had possession of the claimed invention. There are no specific, relevant, identifying characteristics of these markers, and only general methodology is provided with regard to how to identify them. This guidance is insufficient with regard to description of which markers would be expressed or co-detectable with a negative marker or another marker of the mature chondrocyte phenotype.

The skilled artisan could not envision which of the markers, encompassed by the claims, would be expressed, or not expressed, in the cell population instantly claimed, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Accordingly, it is maintained that the claimed invention lacks written description.

Claim Rejections - 35 USC § 112

The prior rejection of claim 43 is withdrawn in view of Applicants' amendment to the claim, which no longer recites "pluripotent".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43, 45 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 is indefinite with regard to the recitation of the term "a purified culture". In particular, the metes and bounds of the term "purified" cannot be ascertained. The term "purified" is a relative term which renders the claim indefinite. The term "purified" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Particularly, the term "purified" is relative with regard to the other components that are present in the culture. Because the claim does not define how pure or what degree or purity the precursor cells must be, the claim is indefinite. This is a new ground of rejection that is necessitated by Applicants' amendment to the claim. Claims 45 and 64 depend from claim 43.

Claim Rejections - 35 USC § 102

The prior rejection of claims 43-45, 61 as being anticipated by Kyoizumi *et al.* is withdrawn in view of Applicants' arguments. Particularly, Kyoizumi teach using whole tissue fragments, and not cultures of cells, or compositions comprising cultured cells, as required by the claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43-44, 61 and newly added claim 64 stand rejected under 35 U.S.C. 102(b) as being anticipated by Takahashi *et al.* (cited previously). This

rejection is maintained for reasons of record, advanced on pages 15-16 of the Office action, mailed 6/27/06.

Applicants' Arguments. Applicants argue that this rejection is rendered moot because Takahashi *et al.* do not describe an isolated population of CDMP-1 positive cells, and that they do not describe the use of this population of cells in a therapeutic composition for the treatment of cartilage defects. See page 22, 1st ¶ of the Response.

Response to Arguments. These arguments have been fully considered but are not persuasive. The claims have been properly interpreted as follows: because the Examiner cannot ascertain the degree/amount of purification of the culture of the viable, differentiated, precursor cells, any amount of purification sufficiently fulfills in the limitations of the claims. Thus, Takahashi's teaching of isolation of human bone marrow aspirates constitutes the purification of the cells with regard to isolating them from a human source. Furthermore, as stated in the prior Office action mailed 6/27/06, p. 15, because the culture, as taught Takahashi, is isolated, as is the instantly claimed culture, from bone marrow, Takahashi's culture would reasonably contain the instantly claimed cells. Because the cells of Takahashi and the cells that are instantly claimed are from the same source (bone marrow), they would necessarily (inherently) express the markers that are required by the claims (CDMP-1, markers co-expressed and/or co-detectable with CDMP-1), and the absence of expression of FGFR3.

Finally, it is reiterated that the phrase "a therapeutic composition" (claims 44, 64) merely sets forth an intended use of the claimed composition and does not serve to further define the compositions. *In re Pearson,* 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974), citing *Kropa v. Robie,* 187 F.2d 150, 88 USPQ 478 (CCPA 1951); *In re Lemin,* 326 F.2d 437, 140 USPQ 273 (CCPA 1964), and *In re Zierden,* 411 F.2d 1325, 162 USPQ 102 (CCPA 1969).

Accordingly, Takahashi *et al.* anticipate the claimed invention.

Claims 43-45, 61 and newly added claims 63 and 64 stand rejected under 35 U.S.C. 102(b) as being anticipated by Erlacher *et al.* (cited previously). This rejection is maintained for reasons of record, advanced on page 16 of the Office action, mailed 6/27/06.

Applicants' Arguments. Applicants argue that Erlacher do not teach the claimed invention, because although they teach cells that express CDMP-1, these cells are found in the cartilage, and not isolated from the periosteum, bone marrow or synovial fluid. Furthermore, because Erlacher do not isolate these cells, nor define their characteristics, they do not anticipate the claimed invention. See page 22, paragraphs 2-3 of Applicants' Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. Firstly, as stated above, because the Examiner cannot ascertain the degree of purification of the culture (claim 43), Erlacher's teaching of the isolation of adult bovine and human articular cartilage cells sufficiently anticipate this aspect of the claimed invention. Furthermore, although Erlacher do not teach that the cells have been isolated from the periosteum, bone marrow or synovial membrane, the source of isolation of the cells fails to distinguish Erlacher's cells from those as instantly claimed, because the expression of CDMP-1 is all that is required by the claim in order to identify the cells.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best,

Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Thus, because Erlacher teach cells that express CDMP-1, they have provided cells with the same characteristics as Applicants' claimed cells. Because Applicants' cells and Erlacher's cells have the identical characteristics, the properties of these cells are inseparable from the cells. Thus, because Erlacher teaches cells that express CDMP-1, these cells would inherently have the characteristics required by the claims, such as being differentiated, pluripotent precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue.

Ehlacher *et al.* anticipate newly added claim 63, which requires that the composition contain a chondrocyte cell composition because they teach that chondrocytes are present in the cultured bovine articular cartilage (p. 265, 2nd col., 2nd ¶) which states that, "Immunohistochemical staining of cultured bovine articular cartilage specimens revealed the presence of the CDMPs in most of the chondrocytes throughout the tissue." Thus, Erlacher provide teachings with regard to a chondrocyte cell population in their composition.

Accordingly, Erlacher *et al.* anticipate the claims.

Claims 43-45, 61 and newly added newly added claims 63 and 64 stand rejected under 35 U.S.C. 102(b) as being anticipated by Chang *et al.* (cited previously). This rejection is maintained for reasons of record, advanced on pages 16-17 of the Office action, mailed 6/27/06.

Applicants' Arguments. Applicants argue that Chang *et al.* show that CDMP-1 postnatally can only be detected in articular and cricoid cartilage, and do not disclose that the cells expression CDMP-1 are isolated from bone marrow, periosteum, or the synovial membrane. Applicants argue that Chang *et al.* have used cells from cartilage, part of which expressed CDMP-1 as an implant in immunocomptent mice, and that they do not disclose a therapeutic composition comprising a precursor cell population expression CDMP-1 obtained from bone marrow, periosteum or the synovial fluid. See pages 22-23 of the Response.

Response to Arguments. These arguments have been fully considered but are not persuasive. As stated above and in the prior Office action, because the Examiner cannot ascertain the degree of purification of the culture (claim 43), Chang's teaching of the isolation cells that express CDMP-1 from articular and cricoid cartilage sufficiently anticipate this aspect of the claimed invention. Indeed, Chang refer to these extracts as "partially purified extracts" (see Abstract). Furthermore, although Chang do not teach that the cells have been isolated from the periosteum, bone marrow or synovial membrane, the source of isolation of the cells fails to distinguish Chang's cells from those as instantly claimed, because the expression of CDMP-1 is all that is required by the claim in order to identify the cells. Finally, it is reiterated, as above, that the term "therapeutic composition" fails to provide patentable weight to the claim, because it merely sets forth an intended use for the composition and does not further define the composition.

Chang anticipate newly added claim 63, which requires that the composition further comprise a chondrocyte cell population, because they teach that

chondrocytes are present in their extracts. Particularly, they teach isolation of RNA from bovine articular chondrocytes (those which are used for the extracts) (see p. 2822, 2nd col., RT-PCR using Degenerate Primers). Accordingly, Chang show that their extracts contain chondrocytes.

Thus, because Chang teach cells that express CDMP-1, they have provided cells with the same characteristics as Applicants' claimed cells. Because Applicants' cells and Chang cells have the identical characteristics, the properties of these cells are inseparable from the cells, and these cells would inherently have the characteristics required by the claims, such as being differentiated, pluripotent precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue.

Accordingly, Chang *et al.* anticipate the claims, because they teach a culture that expresses CDMP-1 and was used as an implant, which is required by the claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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THAIAN N. TON
PATENT EXAMINER